

Benzodiazepine prescriptions on merchant ships without a doctor on board: analysis from medical records of Centro Internazionale Radio Medico (CIRM)

Giulio Nittari¹, Graziano Pallotta¹, Marzio Di Canio², Enea Traini¹, Francesco Amenta^{1, 2}

¹Telemedicine and Telepharmacy Centre, University of Camerino, Camerino, Italy

²Research Department, International Radio Medical Centre (CIRM), Rome, Italy

ABSTRACT

Background: Benzodiazepines are drugs widely used for the treatment of anxiety and insomnia. The present study has analysed the prescriptions of this class of drugs among sailing seafarers, to evaluate the appropriateness of prescribed therapies.

Materials and methods: This study assessed the benzodiazepine prescriptions made by Centro Internazionale Radio Medico (CIRM) doctors from 2011 to 2015. A total of 17,844 medical records were examined. Analysis considered the prescriptions of benzodiazepines in monotherapy, or in association with other drugs. Diagnoses of pathologies for which benzodiazepines were prescribed were made according to the ICD-10 classification system proposed by the World Health Organisation.

Results: Among medical records analysed, benzodiazepines were prescribed in 765 cases (3.29% of total cases assisted by CIRM). Benzodiazepines were prescribed as a single-drug treatment in 626 (81.83%) cases, whereas in 139 cases they were associated with other classes of drugs. In case of opioids prescribed in association with benzodiazepines, the drug used was codeine. This therapeutic association was prescribed in cases of severe pain.

Conclusions: Although the “off label” use of benzodiazepines is not uncommon in medical practice, clear evidence indicates their potential side effects for human health. In this respect, medical professionals should comply with international guidelines on the use of benzodiazepines, both when prescribed as a single drug or in combination with other classes of drugs. These recommendations should be considered seriously in case of limited medical facilities such as on board of sailing ships.

(Int Marit Health 2018; 69, 1: 28–34)

Key words: drug safety, benzodiazepine, drug interactions, ship pharmacy, occupational health

INTRODUCTION

Benzodiazepines are the most frequently prescribed drugs after cardiovascular medications [1]. The effectiveness of the benzodiazepines exceeds the placebo in controlling a wide range of anxiety related symptoms [2, 3] and reducing the onset of insomnia [4]. The use of benzodiazepines for long periods can induce dependence, abuse and symptoms of withdrawal [5, 6]. Based on these risks, several guidelines have warned against the use of benzodiazepines for long periods, especially in older population [7].

The use of benzodiazepines in a multidrug therapy, in particular with opioids, may cause respiratory depression [8]. Concurrent use of oxycodone and benzodiazepines may lead to increased inhibition of the central nervous system and respiratory system [9]. Clinical guidelines from the United States Centres for Disease Control and Prevention recommend the utmost caution in combining opioids and benzodiazepines to avoid possible consequences [10].

In this study we analysed the prescriptions of benzodiazepines among patients on board commercial vessels



without a doctor, and assisted by Centro Internazionale Radio Medico (International Radio Medical Centre [CIRM]). CIRM is the Italian Telemedical Maritime Assistance Service (TMAS) and the Centre with the largest experience in the field, worldwide [11]. In this work, prescriptions of benzodiazepines among seafarers assisted by CIRM from 2011 to 2015 were analysed. Prescriptions were divided into single-drug prescriptions (benzodiazepines were the only prescribed drug) and multi-drug prescriptions (benzodiazepines in association with other medicines).

Seafarers represent a category of workers particularly exposed to physical and mental stress. For such a reason we decided to evaluate the appropriateness of benzodiazepine prescriptions among them, and to assess the effective compliance of the advice with standard pharmacotherapy guidelines.

MATERIALS AND METHODS

This study analysed benzodiazepine prescriptions performed by CIRM physicians from 1st January 2011 to 31st December 2015. For each case assisted by the Centre, a digitalised medical file is established and updated after any contact with the ship. These files represented the basis of this study.

All seafarers gave their informed consent for the treatment of their medical data by CIRM. According to the informed consent policy, data were anonymised before being used for research purposes. This survey is a part of the project called “Health Protection and Safety on Board Ships” (acronym: HEALTHY SHIP). It is a project of disease prevention and health protection approved by the CIRM Foundation Ethic Committee [12].

The investigation was performed by reviewing 17,844 health records of patients assisted by CIRM during the period indicated above. Among these, 632 were excluded because they were related to advice on hygiene or pharmacy management. The remaining 17,212 medical records were considered for this study and the diagnosis of CIRM physicians was classified according to the International Classification of Diseases, 10th edition (ICD-10) [8]. This standard is used worldwide for the general epidemiology, health management and clinical analysis.

After this first evaluation, medical files containing benzodiazepine prescriptions were extrapolated and examined. Considering the different clinical implications that a multi-drug therapy with benzodiazepines may involve (compared to a single-drug therapy), cases in which benzodiazepines were the only drug prescribed were extrapolated from cases in which benzodiazepines were prescribed in combination with other classes of drugs.

The demographic data of the people assisted and receiving benzodiazepine prescriptions were considered. Our sam-

ple consisted for the most part of male subjects employed on board merchant ships aged between 18 and 64 years (mean 38.5 ± 11.6 years). A small percentage (52 cases) was represented by women and children. They did not have benzodiazepines prescribed. Analysis did not consider the rank of people receiving benzodiazepine prescription or the flag of the ship where they worked.

In a second step, the prescriptions of benzodiazepines were compared to the diagnosis of the problem for which they were given. This was done in order to evaluate the compliance of the prescription with guidelines for their use.

RESULTS

Benzodiazepine prescribed for pathologies classified according to the ICD-10 are summarised in Table 1.

As shown, benzodiazepines were prescribed in 765 cases (3.29% of total cases assisted by CIRM). Benzodiazepines were prescribed as a single-drug treatment in 626 cases (81.83%), whereas in 139 cases they were associated with other therapeutic agents (Table 2). As shown in Table 2, benzodiazepines were more often associated with opioids (16.8%), followed by non-steroidal anti-inflammatory drugs (NSAID) (Table 2).

Analysis of benzodiazepine prescriptions (as a monotherapy) during the 5 years of observation has shown a significant increase in their number from 2011 to 2012. Prescriptions of benzodiazepines plateaued from 2012 to 2014 and then slightly decreased (Fig. 1). Analysis of prescriptions of benzodiazepines in combination with other classes of drugs is summarised in Table 2.

As shown the most common association was with codeine followed in descending order by different NSAID (e.g. acetylsalicylic acid, ibuprofen, diclofenac and nimesulide) and by paracetamol.

Prescriptions of benzodiazepines in association with codeine were analysed carefully in view of the risks of combining these drugs [10]. In the first year of observation (2011), the drug combination of diazepam and codeine was found 123 times (Fig. 2). In the subsequent years the prescription rate of this association dropped to 0 (Fig. 2).

Analysis of prescriptions of benzodiazepines according to diagnosis showed that for the ICD-10 class V diseases (mental and behavioural disorders) we had 111 benzodiazepine prescriptions (89 in single drug therapy and 22 in association with codeine) (Fig. 3). This accounts for the 64.53% of cases diagnosed with this class of diseases (Table 1). Pathologies for which benzodiazepines were prescribed included anxiety (36 cases), depression (27 cases), psychomotor agitation (21 cases) and behavioural disorders (19 cases).

For class VI (diseases of the nervous system) benzodiazepines were prescribed in 110 cases (99 in single-prescription, 8 associated with codeine and 3 as-

Table 1. Diagnosis (ICD-10) of diseases for which benzodiazepines were prescribed from 2011–2015

ICD-10	Total cases assisted	No. of cases with benzodiazepines prescriptions	Per cent
I. Certain infectious and parasitic diseases	670	3	0.45%
II. Neoplasms	2	0	0%
III. Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	60	0	0%
IV. Endocrine, nutritional and metabolic diseases	172	3	1.74%
V. Mental and behavioural disorders	172	111	64.53%*
VI. Diseases of the nervous system	577	110	19.065%*
VII. Diseases of the eye and adnexa	639	3	0.47%
VIII. Diseases of the ear and mastoid process	231	3	1.30%
IX. Diseases of the circulatory system	1227	279	22.74%*
X. Diseases of the respiratory system	885	15	1.70%
XI. Diseases of the digestive system	3261	43	1.32%
XII. Diseases of the skin and subcutaneous tissue	1690	9	0.53%
XIII. Diseases of the musculoskeletal system and connective tissue	1243	51	4.10%
XIV. Diseases of the genitourinary system	1595	20	1.25%
XV. Pregnancy, childbirth and the puerperium	52	0	0%
XVI. Certain conditions originating in the perinatal period	0	0	0%
XVII. Congenital malformations, deformations and chromosomal abnormalities	15	1	Not quantifiable for insufficient number of cases
XVIII. Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1279	74	5.79%*
XIX. Injury, poisoning and certain other consequences of external causes	3207	37	1.15%
XX. External causes of morbidity and mortality	58	0	0%
XXI. Factors influencing health status and contact with health services	177	3	1.69%

*Asterisk indicates classes of pathologies with the larger use of benzodiazepine prescriptions.

Table 2. Different benzodiazepines prescribed in monotherapy and in association with other therapeutic agents

Benzodiazepine molecule prescribed	N (%)
Diazepam	622 (81.31%)
Nitrazepam	2 (0.26%)
Alprazolam	1 (0.13%)
Clonazepam	1 (0.13%)
Benzodiazepines in association	N (%)
Diazepam + codeine	123 (16.08%)
Diazepam + acetylsalicylic acid	8 (1.05%)
Diazepam + paracetamol (acetaminophen)	3 (0.39%)
Diazepam + ibuprofen	3 (0.39%)
Diazepam + diclofenac	1 (0.13%)
Diazepam + nimesulide	1 (0.13%)

Data were derived from analysis of the 765 clinical records using benzodiazepines.

sociated with NSAIDs) (Fig. 3). Hence benzodiazepines were prescribed in the 19.06% of cases of this class of disease (Table 1).

Figure 3 summarises the different ICD-10 classes of diseases for which benzodiazepine were prescribed alone in combination. Disease categories for which benzodiazepines were highly prescribed are highlighted in red with an asterisk in Table 1.

For class IX ICD-10 (diseases related to the cardiovascular system) benzodiazepines were prescribed 241 times (225 in monotherapy, 50 in combination with codeine and 4 in association with NSAIDs) (Fig. 3). In summary, benzodiazepines were given to 22.74% of cases of these class of diseases (Table 1). Pathologies for which benzodiazepines were mostly prescribed included arterial hypertension (131 cases), precordial pain (122 cases) and tachycardia (13 cases).

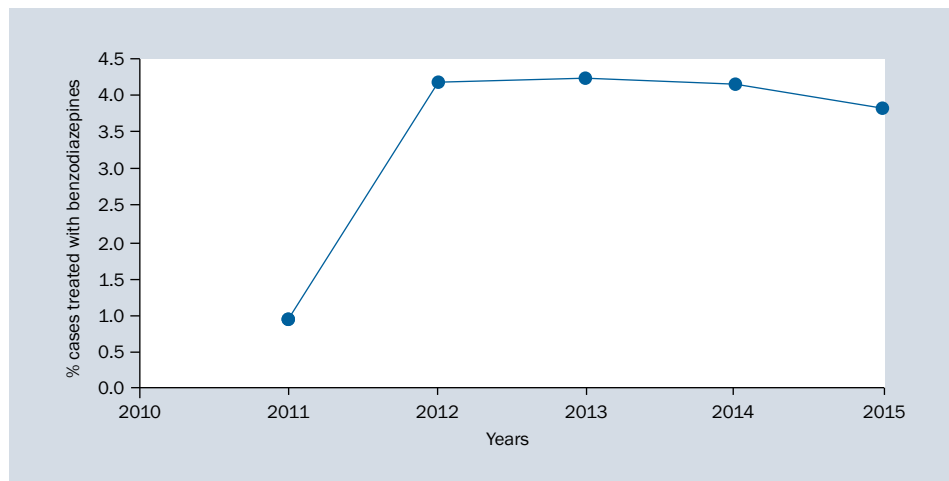


Figure 1. Time-course of single-drug prescriptions of benzodiazepines

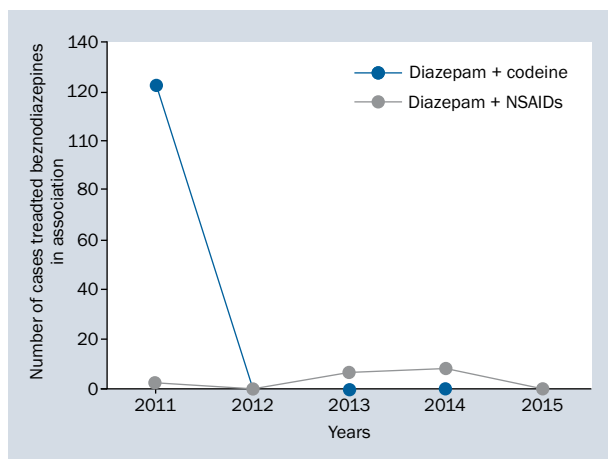


Figure 2. Time-trend of prescriptions of benzodiazepines in multi-drug therapies; NSAIDs – non-steroidal anti-inflammatory drugs

For class XIII (diseases of the musculoskeletal system and connective tissue) the total percentage of benzodiazepines averaged the 4.10% (51 prescriptions of benzodiazepines) (Table 1). In this class of diseases benzodiazepines were prescribed as a single-drug in 41 cases, 7 times in association with opioids and 3 times in association with NSAIDs (Fig. 3). Prescriptions were for low back pain (31 cases) and neck pain (14 cases).

For the ICD-10 class XVIII (symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified) the percentage of total prescriptions of benzodiazepines averaged to 5.79% (Table 1), with a total of 74 prescriptions of benzodiazepines (56 single-drug therapy, 15 in combination with codeine and 3 in association with NSAIDs) (Fig. 3). Weakness and fatigue (63 cases) were the main reason for prescribing benzodiazepines in this class of diseases.

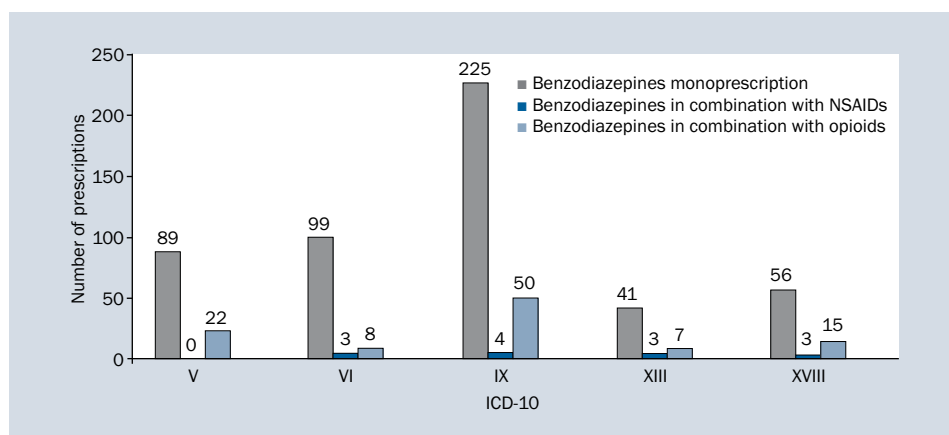


Figure 3. Benzodiazepine prescriptions in single-drug and in combination therapies, in the different classes of diseases for which there drugs were mainly used; NSAIDs – non-steroidal anti-inflammatory drugs

DISCUSSION

The analysis of data revealed a common trend of benzodiazepine prescriptions among seafarers. Despite the risks associated with the use of this class of drugs (falls [13], fractures, accidents at work [14–19]), the utilisation of benzodiazepines increased during the 5 years of observation, with an estimated increase of more than 400% between 2011 and 2012, an increase less pronounced in 2013 and a slight decline in 2014 and 2015 (Fig. 1). Anxiety (36%) and insomnia (44%) represented the most common diagnoses for the prescription of benzodiazepines [20–22]. Clinical guidelines recommend that benzodiazepines and other hypnotics should only be used in short-term treatment for severe insomnia and only be used after careful consideration of the non-pharmacological options such as behavioural interventions like sleep education, stimulus control [23]. New guidelines recommend newer anti-depressants [24], in substitution of benzodiazepines for the primary treatment of anxiety disorders [25]. Although many physicians are aware of the indications and warnings provided by the guidelines that warn against the unjustified use of benzodiazepines, in particular in long-term therapy, a few of them believe that this practice constitutes a serious risk for their patients [26].

The problem of pharmacological treatment of patients and diseases on board ships is complex for several reasons. The first is that, as already mentioned in the introduction, with the exception of cruise ships or large passenger ships in some countries, other merchant ships do not carry on board neither doctors nor other qualified health professionals. Treatment of diseases or accidents is left to the responsibility of the captain who could be supported by TMAS [27, 28]. However, even more recent international recommendations leave to the captain the final responsibility of choices or of treatment [28]. A principle rather questionable taking into account the rudimentary medical knowledge of a ship's captain [29, 30]. The second is the limited availability of medicinal products carried on board ships. Every ship, even small ships and those covering short distances, should have a minimum supply of medicinal products and medication items that constitute the so-called ship's medicine chest [27]. The World Health Organisation [31], the European Economic Community [32] and the main maritime countries have regulated the contents of ship's medicine chest. These may differ considerably in the number and typology of medicinal products and other supplies. This may limit the prescription of effective treatments normally used by a doctor. Hence, apparent inappropriate prescriptions may depend by the lack of availability on board of the most appropriate medicinal products.

Diseases of cardiovascular system (ICD-10 class IX) were those for which benzodiazepines were more prescribed from a quantitative point of view, followed by mental and

behavioural disorders (ICD-10 class V), symptoms, signs and abnormal clinical and laboratory findings (ICD-10 class XVIII), diseases of the musculoskeletal system (ICD-10 class XIII) and of the nervous system (ICD-10 class VI). In terms of percentage of benzodiazepine prescriptions referred to the number of patients suffering from a given class of diseases, benzodiazepines were given more often for mental and behavioural disorders, followed by diseases of the circulatory system, nervous system, symptoms and diseases of the musculoskeletal system. The main ICD-10 classes in which benzodiazepines were prescribed in monotherapy or in association; during the period under study were classes V, VI, IX, XIII and XVIII.

In class V, mental and behavioural disorders, benzodiazepines were mainly used for anxiety, depression, psychomotor agitation and behavioural disorders. Often due to lack of more specific drugs, aboard ships, for depressive disorders, the use of anxiolytics in depressive disorders continues to be of interest, since depression has a close relationship with anxiety [33].

In class VI, diseases of the nervous system, benzodiazepines were mostly used to treat insomnia, sciatica, headache, epileptic seizure and paraesthesia.

Data of class IX (diseases of the circulatory system) show the wide (over 100 cases) use of benzodiazepines in the treatment of hypertension and precordial pain. In this respect, it has been reported that benzodiazepines have hypotensive action through a central mechanism that acts on arterial baroreflex or the sympathetic and vagal outflow. Other researchers attribute the hypotensive action of benzodiazepines to their vasodilatory effect or its effect on peripheral benzodiazepine receptors, suggesting a peripheral mechanism [34, 35].

In class XIII, diseases of the musculoskeletal system and connective tissue, benzodiazepines are mostly used for low back and neck pain. GABAergic compounds enhance endogenous inhibitory control within the central nervous system and are therefore potentially useful in human pain conditions. In particular, a study showed the analgesic effect of clobazam in low back pain [36].

Finally, in class XVIII, symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, we observed a high use of benzodiazepines in cases of weakness and fatigue. This is interesting, as weakness and fatigue are common adverse effects of benzodiazepines. Probably, in this case, the use of benzodiazepines was related with their sedative effects, which could result in the promotion of rest and subsequent recovery of the patient. Anyhow, the appropriateness of this use may be questioned, and it is another example of how the lack of more specific drugs in the ship's pharmacy can determine the prescription of second-choice treatments.

Clinical guidelines from the United States Centres for Disease Control and Prevention, suggest the utmost caution concerning the concurrent use of opioids and benzodiazepines, to avoid possible serious consequences [8, 10]. In this study, it was observed that between 2011 and 2012 treatment with diazepam in combination with codeine was prescribed 123 times (Fig. 2). In subsequent years, from 2013 to 2015, this drug combination was no longer prescribed. The use of this drug combination was mainly prescribed for diseases of class IX (diseases of the cardiovascular system) with a total number of 42 prescriptions, 24 prescriptions for class V (diseases related to mental and behavioural disorders), 21 prescriptions for class XVIII (diseases diagnosed by symptoms, signs and abnormal clinical and laboratory tests, diseases that can't be classified in other classes) and 12 prescriptions for class XIII (diseases related to the musculoskeletal system and connective tissue (Fig. 3). The ship's medicine chest often lacks of in specific drugs, primarily those indicated for certain classes of less considered. This could explain the "off label" use of benzodiazepines on board ships.

CONCLUSIONS

Although the "off label" use of benzodiazepines is reflected in medical practice, clear scientific evidence exists for potential side effects of these drugs for human health. In this respect, medical professionals should rigidly comply with international guidelines in the use of benzodiazepines, both when prescribed as a single drug or in combination with other classes of drugs. Real-time monitoring programmes can help physicians to make more appropriate decisions when prescribing this sensitive class of drugs. A review of the regulations on drugs and medicines that commercial ships should carry expanding medical chests based on the actual incidence rates of on-board conditions would allow doctors to have a wider choice in the prescribing pharmacological treatments. The safe use of benzodiazepines in the ship's environment, where any intervention reducing concentration and alertness could be risky will be possible if seafarers, their doctors, ship owners, and international organisations will work together and act balancing advantages and potential problems in the use of this class of drugs.

ACKNOWLEDGEMENTS

We would like to thank CIRM and Department of Telemedicine and Telepharmacy of the University of Camerino, Italy.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Comitato etico-scientifico-medico of CIRM Foundation.

FUNDING

This study was supported by CIRM Rome and University of Camerino, Centre of Telemedicine and Telepharmacy.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Woods JH, Katz JL, Winger G. Benzodiazepines: use, abuse, and consequences. *Pharmacol Rev.* 1992; 44(2): 151–347, indexed in Pubmed: [1356276](#).
2. Martin JL, Sainz-Pardo M, Furukawa TA, et al. Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials. *J Psychopharmacol.* 2007; 21(7): 774–782, doi: [10.1177/0269881107077355](#), indexed in Pubmed: [17881433](#).
3. Balkom AJ, Bakker A, Spinhoven P, et al. A Meta-Analysis of the Treatment of Panic Disorder with or without Agoraphobia: A Comparison of Psychopharmacological, Cognitive-Behavioral, and Combination Treatments. *J Nerv Ment Dis.* 1997; 185(8): 510–516, doi: [10.1097/00005053-199708000-00006](#), indexed in Pubmed: [9284865](#).
4. Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med.* 2007; 22(9): 1335–1350, doi: [10.1007/s11606-007-0251-z](#), indexed in Pubmed: [17619935](#).
5. Rickels K, Schweizer E, Case WG, et al. Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. *Arch Gen Psychiatry.* 1990; 47(10): 899–907, doi: [10.1001/archpsyc.1990.01810220015002](#), indexed in Pubmed: [2222129](#).
6. Fenton MC, Keyes KM, Martins SS, et al. The role of a prescription in anxiety medication use, abuse, and dependence. *Am J Psychiatry.* 2010; 167(10): 1247–1253, doi: [10.1176/appi.ajp.2010.09081132](#), indexed in Pubmed: [20595413](#).
7. American Psychiatric Association Task Force on Benzodiazepine Dependency. *Benzodiazepine Dependency, Toxicity, and Abuse.* American Psychiatric Publishing, Arlington 1990.
8. Abernethy DR, Greenblatt DJ, Steel K, et al. Impairment of hepatic drug oxidation by propoxyphene. *Ann Intern Med.* 1982; 97(2): 223–224, doi: [10.7326/0003-4819-97-2-223](#), indexed in Pubmed: [7103282](#).
9. Product Information: OxyContin(R) oral controlled-release tablets, oxycodone HCl oral controlled-release tablets. Purdue Pharma L.P. (for FDA), Stamford, CT, Apr, 2013.
10. U.S. Food and Drug Administration 10903 New Hampshire Avenue Silver Spring, MD 20993 1-888-INFO-FDA(1-888-4636332). <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518697.htm>.
11. Mahdi SS, Amenta F. Eighty years of CIRM. A journey of commitment and dedication in providing maritime medical assistance. *Int Marit Health.* 2016; 67(4): 187–195, doi: [10.5603/IMH.2016.0036](#), indexed in Pubmed: [28009394](#).
12. Ricci G, Cannovo R. The importance of the training of Ethics Committee members. *Med Law.* 2009; 28(4): 649–659, indexed in Pubmed: [20157976](#).
13. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* 2009; 169(21): 1952–1960, doi: [10.1001/archinternmed.2009.357](#), indexed in Pubmed: [19933955](#).

14. Wagner AK, Zhang F, Soumerai SB, et al. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? *Arch Intern Med.* 2004; 164(14): 1567–1572, doi: [10.1001/archinte.164.14.1567](https://doi.org/10.1001/archinte.164.14.1567), indexed in Pubmed: [15277291](https://pubmed.ncbi.nlm.nih.gov/15277291/).
15. Kjosavik SR, Ruths S, Hunskaar S. Psychotropic drug use in the Norwegian general population in 2005: data from the Norwegian Prescription Database. *Pharmacoepidemiol Drug Saf.* 2009; 18(7): 572–578, doi: [10.1002/pds.1756](https://doi.org/10.1002/pds.1756), indexed in Pubmed: [19402032](https://pubmed.ncbi.nlm.nih.gov/19402032/).
16. Cascade E, Kalali AH. Use of benzodiazepines in the treatment of anxiety. *Psychiatry (Edgmont).* 2008; 5(9): 21–22, indexed in Pubmed: [19727256](https://pubmed.ncbi.nlm.nih.gov/19727256/).
17. Hoggan DB, Maxwell CJ, Fung TS, et al. Canadian Study of Health and Aging. Prevalence and potential consequences of benzodiazepine use in senior citizens: results from the Canadian Study of Health and Aging. *Can J Clin Pharmacol.* 2003; 10(2): 72–77, indexed in Pubmed: [12879145](https://pubmed.ncbi.nlm.nih.gov/12879145/).
18. Petitjean S, Ladewig D, Meier CR, et al. Benzodiazepine prescribing to the Swiss adult population: results from a national survey of community pharmacies. *Int Clin Psychopharmacol.* 2007; 22(5): 292–298, doi: [10.1097/YIC.0b013e328105e0f2](https://doi.org/10.1097/YIC.0b013e328105e0f2), indexed in Pubmed: [17690598](https://pubmed.ncbi.nlm.nih.gov/17690598/).
19. Bolton JM, Metge C, Lix L, et al. Fracture risk from psychotropic medications: a population-based analysis. *J Clin Psychopharmacol.* 2008; 28(4): 384–391, doi: [10.1097/JCP.0b013e31817d5943](https://doi.org/10.1097/JCP.0b013e31817d5943), indexed in Pubmed: [18626264](https://pubmed.ncbi.nlm.nih.gov/18626264/).
20. Simon GE, Ludman EJ. Outcome of new benzodiazepine prescriptions to older adults in primary care. *Gen Hosp Psychiatry.* 2006; 28(5): 374–378, doi: [10.1016/j.genhosppsy.2006.05.008](https://doi.org/10.1016/j.genhosppsy.2006.05.008), indexed in Pubmed: [16950371](https://pubmed.ncbi.nlm.nih.gov/16950371/).
21. Manthey L, Giltay EJ, van Veen T, et al. Determinants of initiated and continued benzodiazepine use in the Netherlands study of depression and anxiety. *J Clin Psychopharmacol.* 2011; 31(6): 774–779, doi: [10.1097/JCP.0b013e3182362484](https://doi.org/10.1097/JCP.0b013e3182362484), indexed in Pubmed: [22020355](https://pubmed.ncbi.nlm.nih.gov/22020355/).
22. Luijendijk HJ, Tiemeier H, Hofman A, et al. Determinants of chronic benzodiazepine use in the elderly: a longitudinal study. *Br J Clin Pharmacol.* 2008; 65(4): 593–599, doi: [10.1111/j.1365-2125.2007.03060.x](https://doi.org/10.1111/j.1365-2125.2007.03060.x), indexed in Pubmed: [18093258](https://pubmed.ncbi.nlm.nih.gov/18093258/).
23. Jorm AF, Grayson D, Creasey H, et al. Long-term benzodiazepine use by elderly people living in the community. *Aust N Z J Public Health.* 2000; 24(1): 7–10, doi: [10.1111/j.1467-842x.2000.tb00715.x](https://doi.org/10.1111/j.1467-842x.2000.tb00715.x), indexed in Pubmed: [10777971](https://pubmed.ncbi.nlm.nih.gov/10777971/).
24. Fourrier A, Letenneur L, Dartigues JF, et al. Benzodiazepine use in an elderly community-dwelling population. Characteristics of users and factors associated with subsequent use. *Eur J Clin Pharmacol.* 2001; 57(5): 419–425, doi: [10.1007/s002280100326](https://doi.org/10.1007/s002280100326), indexed in Pubmed: [11599660](https://pubmed.ncbi.nlm.nih.gov/11599660/).
25. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA.* 2003; 289(9): 1107–1116, doi: [10.1001/jama.289.9.1107](https://doi.org/10.1001/jama.289.9.1107), indexed in Pubmed: [12622580](https://pubmed.ncbi.nlm.nih.gov/12622580/).
26. National Institute for Clinical Excellence. Guidance on the Use of Zaleplon, Zolpidem and Zopiclone for the Short-term Management of Insomnia, Technology Appraisal 77. London, England: NICE; 2004. London, 2004.
27. Goethe WHG, Watson EN, Jones DT. Handbook of Nautical Medicine. Springer-Verlag, Berlin 1984.
28. International Maritime Organization: Medical Assistance at sea. MSC/Circ.960 Ref. T1/3.02 London SE1 7SR 20 June 2000.
29. Ricci G, Pirillo I, Rinuncini C, et al. Medical assistance at the sea: legal and medico-legal problems. *Int Marit Health.* 2014; 65(4): 205–209, doi: [10.5603/IMH.2014.0039](https://doi.org/10.5603/IMH.2014.0039), indexed in Pubmed: [25522704](https://pubmed.ncbi.nlm.nih.gov/25522704/).
30. Ricci G, Pirillo I, Amenta F. Ethical challenges to medical assistance at sea. *Marine Policy.* 2017; 81: 247–249, doi: [10.1016/j.marpol.2017.04.007](https://doi.org/10.1016/j.marpol.2017.04.007).
31. Cook JM, Biyanova T, Masci C, et al. Older patient perspectives on long-term anxiolytic benzodiazepine use and discontinuation: a qualitative study. *J Gen Intern Med.* 2007; 22(8): 1094–1100, doi: [10.1007/s11606-007-0205-5](https://doi.org/10.1007/s11606-007-0205-5), indexed in Pubmed: [17492325](https://pubmed.ncbi.nlm.nih.gov/17492325/).
32. Bursztajn HJ, Brodsky A. Ethical and legal dimensions of benzodiazepine prescription: a commentary. *Psychiatr Ann.* 1998; 28(3): 121–127, doi: [10.3928/0048-5713-19980301-06](https://doi.org/10.3928/0048-5713-19980301-06), indexed in Pubmed: [15739288](https://pubmed.ncbi.nlm.nih.gov/15739288/).
33. Paul SM. Anxiety and depression: A common neurological substrate? *J Clin Psychiatry.* 1988; 49(suppl): 13–16.
34. French JF, Rapoport RM, Matlib MA. Possible mechanism of benzodiazepine-induced relaxation of vascular smooth muscle. *J Cardiovasc Pharmacol.* 1989; 14(3): 405–411, doi: [10.1097/00005344-198909000-00008](https://doi.org/10.1097/00005344-198909000-00008), indexed in Pubmed: [2476619](https://pubmed.ncbi.nlm.nih.gov/2476619/).
35. Gifford RW. Management of hypertensive crises. *JAMA.* 1991; 266(6): 829–835, doi: [10.1001/jama.266.6.829](https://doi.org/10.1001/jama.266.6.829), indexed in Pubmed: [1865522](https://pubmed.ncbi.nlm.nih.gov/1865522/).
36. Chou R, Huffman LH. American Pain Society, American College of Physicians. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med.* 2007; 147(7): 505–514, doi: [10.7326/0003-4819-147-7-200710020-00008](https://doi.org/10.7326/0003-4819-147-7-200710020-00008), indexed in Pubmed: [17909211](https://pubmed.ncbi.nlm.nih.gov/17909211/).