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INTEGRATIVE REVIEW ARTICLE

USE OF BENZODIAZEPINES AND THEIR IMPLICATIONS: AN INTEGRATIVE REVIEW

USO DE BENZODIAZEPÍNICOS E SUAS IMPLICAÇÕES: REVISÃO INTEGRATIVA USO DE BENZODIAZEPINAS Y SUS IMPLICACIONES: UNA REVISIÓN INTEGRADORA

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ABSTRACT

Objective: analyzing the scientific literature about the use of benzodiazepines. **Method:** an integrative review, in order to answering the question << **What are the generalizations that we can do about the studies on the use of benzodiazepines?** >>, with data collection in the LILACS and MEDLINE databases, from 2008 to 2012, using the descriptors: benzodiazepines, psychoactive drugs and pharmacoepidemiology. To analyzing the articles sought to the units of meaning that make up the corpus of 51 selected articles. **Results:** in the population, the prevalence of benzodiazepine use in different populations ranged from 6,9% to 14% in the general population, and among elderly varies from 9,2% to 13,8%. These values vary according to the method of obtaining data, averaging 12% for primary source (involving 27-749 individuals) and 9,1% for studies with secondary source (1.192-30.000 participants). **Conclusion:** the studies describe the prevalence and profile of users of benzodiazepines, but do not explore the practices and motivations for their use. This makes difficult the establishment of generalizations that may serve to planning of prevention action and the rational use of these medicines. **Descriptors:** Benzodiazepines; Psychoactive Drugs; Pharmacoepidemiology.

RESUMO

Objetivo: analisar a produção científica sobre o uso de benzodiazepínicos. **Método:** revisão integrativa, com vistas a responder a questão norteadora << **Quais as generalizações que podemos fazer acerca dos estudos sobre uso de benzodiazepínicos?** >>, com levantamento de dados nas bases LILACS e MEDLINE, no período de 2008 a 2012, utilizando os descritores: benzodiazepinas, psicofármacos e farmacoepidemiologia. Para a análise dos artigos buscou-se os núcleos de sentido que compõem o *corpus* de 51 artigos selecionados. **Resultados:** na população, a prevalência do uso de benzodiazepínicos em diferentes populações variou de 6,9% e 14% na população geral e, entre idosos, varia de 9,2% a 13,8%. Esses valores variam segundo o método de obtenção de dados, sendo em média de 12% para fonte primária (envolvendo de 27 a 749 indivíduos) e 9,1% para estudos com fonte secundária (de 1.192 a 30.000 participantes). **Conclusão:** os estudos descrevem a prevalência e perfil dos usuários de benzodiazepínicos, mas não exploram as práticas e motivações para sua utilização. Isto dificulta o estabelecimento de generalizações que possam servir ao planejamento de ações de prevenção e uso racional desses medicamentos. **Descritores:** Benzodiazepínicos; Psicofármacos; Farmacoepidemiologia.

RESUMEN

Objetivo: analizar la literatura científica acerca del uso de las benzodiazepinas. **Método:** una revisión integradora, con el fin de responder a la pregunta << **¿Cuáles son las generalizaciones que podemos hacer acerca de los estudios del uso de benzodiazepinas?** >>, con la recogida de datos en las bases de datos LILACS y MEDLINE, de 2008 a 2012, utilizando los descriptors: benzodiazepinas, drogas psicoactivas y farmacoepidemiología. Para el análisis de los artículos buscó a las unidades de significado que constituyen el corpus de 51 artículos seleccionados. **Resultados:** en la población, la prevalencia del consumo de benzodiazepinas en diferentes poblaciones varió de 6,9% a 14% en la población general, y entre los ancianos varió de 9,2% a 13,8%. Estos valores varían de acuerdo con el método de obtención de datos, con un promedio de 12% para la fuente primaria (que implica 27 a 749 individuos) y 9,1% para los estudios con fuente secundaria (1.192-30.000 participantes). **Conclusión:** los estudios describen la prevalencia y el perfil de los usuarios de las benzodiazepinas, pero no exploran las prácticas y motivaciones para su uso. Esto dificulta el establecimiento de generalizaciones que pueden servir la planificación de la prevención y el uso racional de estos medicamentos. **Descriptor:** Benzodiazepinas; Psicofármacos; Farmacoepidemiología.

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INTRODUCTION

One of the major challenges for the next decade as part of public health policies with respect to inappropriate and indiscriminate use of medicines.¹ Among the medicines that require certain care during their use are the benzodiazepines that, according to Decree 344/98² of the National Health Surveillance Agency (Anvisa), are psychotropic drugs subjected to special control. About the use of such products, a population study conducted in Australia showed that between 2000 and 2006 the use of benzodiazepines increased in 22% in that population.³ In Brazil, in the first national household survey, conducted in 2001, 3,3% of respondents said use of benzodiazepines and, in 2006, another survey showed the use of these drugs by 5,6% of respondents.⁴ These data show the increased use of drugs of this class and reinforce the importance of understanding the factors associated with prevalence of these changes.

Benzodiazepines have sedative properties and are used as hypnotics, anxiolytics, anticonvulsants, muscle relaxants and for the treatment of alcohol detoxification.⁵ The use of this class of drugs for a period greater than four to six weeks may lead to the development of tolerance, addiction and dependence.⁶ According to the World Health Organization - WHO, addiction is defined as the "psychic state, and sometimes physical, caused by the interplay between a living organism and a drug, which is characterized by behavioral changes and other reactions always comprise an uncontrollable urge to take the drug in a continuous or periodic basis in order to experience its psychic effects, and in some cases, to avoid the discomfort produced by deprivation".⁷ Its cause is explained by factors including variables related to the drug (higher doses, prolonged use of short half life time, screeching halt use) and related to the patient (comorbidity between depression and anxiety, neurosis, panic attacks and background abuse of alcohol or other substances).⁵

The WHO estimated that over 50% of all drugs are incorrectly prescribed, dispensed and sold; and more than half of patients use them incorrectly.⁸ In Brazil, where the growth of the elderly population is at an unprecedented level, the use of drugs by them should be the subject of specific policy due to aging own changes.⁹ Inadequate consumption pattern of drugs associated with disease and aging own changes, constantly triggers side effects and drug interactions with serious consequences constitutes a

serious problem. The use of the Beers-Fick¹⁰ criteria for identifying potentially inappropriate prescriptions (PPI) in the elderly, it was established that benzodiazepines are among the most prescribed drugs and the use reaches 7% to 37,6% of this population.¹¹

It becomes necessary, therefore, understanding the phenomenon of the use of benzodiazepines by the people, because the chronic and/or indiscriminate use of these drugs can lead to the appearance of iatrogenic and cause serious damage to health and often use is made by the people without aware of their potential risks.

OBJECTIVE

- Analyzing the publications to clarify how the studies have approached the issue of use of benzodiazepines.

METHOD

Article drawn from the dissertation << *The use of benzodiazepines in Paraíba populations: the influence of kinship relations* >> presented to the Postgraduate Program in Public Health of the State University of Paraíba/UEPB. Campina Grande-PB, Brazil. 2014.

There was used a resource of evidence-based practice¹²⁻³, the integrative review, considered a specific method that summarizes the past empirical or theoretical literature, to provide a more comprehensive understanding of a certain phenomenon.⁴ The review was conducted using six basic steps: the first step was to define the guiding research question; in the second step there were defined the inclusion and exclusion criteria; in the third step there were elected databases and held the pursuit of scientific productions; in the fourth step there was elected the data analysis; in the fifth step is designed to discuss the data; and in the sixth step synthesis of the review was presented.¹³

The guiding question of the study was: What are the generalizations we can make about the studies on use of benzodiazepines?

Thus, there was employed in inclusion criteria: population-based studies that exclusively addressed the use of psychotropic drugs (including benzodiazepines) and/or exclusively benzodiazepines; articles that make available the full text online version of free manner; and national and international productions, published in Portuguese, Spanish or English, classified in strata A and B of WebQualis of Public Health. The enclosed timeline were the years 2008-2012 in order to

portray today's scientific production. Thesis were excluded, dissertations, monographs and articles that treat populations with hospitalized or institutionalized participants because we believe that they use more often and in greater quantities, the drugs in question because they have more severe and therefore giving biases in study results. They also excluded after reading the summary, studies that did not converge with the proposed subject matter, beyond the publications that were repeated in the databases.

The search was conducted by two reviewers, ensuring rigor in the selection process of the articles in the databases LILACS and MEDLINE in the second half of 2013, with descriptors standardized and available in the Descriptors in Health Sciences (DeCS): "benzodiazepines" [and] "psychotropic drugs" [and] "pharmacoepidemiology."

After reading the titles and abstracts, selected studies were analyzed using an instrument developed by the authors, evaluating data on the type of study, methods used, population and sample, primary objective, data sources used, study site , summary of results and the level of evidence¹²: 1 - systematic reviews or meta-analysis of relevant clinical trials; 2 - evidence of at least one randomized controlled clinical trial clearly delineated; 3 - well-designed clinical trials without randomization; 4 - cohort studies and well-designed case-control; 5 - systematic review of descriptive and qualitative studies; 6 - evidence derived from a single descriptive or qualitative study; 7 -

authorities of opinion or expert committees including information not interpretations based on researches.¹³

Through thematic analysis or categorical type of content analysis technique, operated to break up the text into units (categories), according to analog systematic regroupings.¹⁴

The analysis is made up by reading the 51 articles selected, later sought to discover the units of meaning that make up the corpus of the study, concerned with the frequency of these cores, as targetable and similar data where it made a new analysis and they emerged three categories respectively: general characteristics of the studies; the use of benzodiazepines in numbers; and practices of use of benzodiazepines and its consequences.

RESULTS

Among the selected studies, it can be observed using two types of designs, the cross-sectional (36) and longitudinal (15). Between the longitudinal studies there is a predominance of cohort studies (13) followed by case-control studies (2). Regarding the approach, all adopted quantitative approaches making it difficult, or impossible, understanding more subjective aspects related to the use of benzodiazepines (Table 1). The data were through primary collection (29) and secondary data (18) coming from databases. Four studies used primary and secondary sources.

Code	Year	Place	Type of study	Evidence level
A1	2008	Brazil	Descriptive	VI
A2	2008	France	Case-control	IV
A3	2008	Spain	Descriptive	VI
A4	2008	Holland	Case-control	IV
A5	2009	Brazil	Cohort	IV
A6	2009	Austria	Cohort	IV
A7	2009	France	Cohort	IV
A8	2009	Spain	Descriptive	VI
A9	2009	Taiwan	Descriptive	VI
A10	2009	Sweden	Descriptive	VI
A11	2009	Norway	Descriptive	VI
A12	2009	Mexico	Descriptive	VI
A13	2009	Australia	Descriptive	VI
A14	2009	Holland	Descriptive	VI
A15	2009	Chile	Descriptive	VI
A16	2010	France	Cohort	IV
A17	2010	Canada	Descriptive	VI
A18	2010	Canada	Descriptive	VI
A19	2010	Brazil	Descriptive	VI
A20	2010	Australia	Descriptive	VI
A21	2010	France	Descriptive	VI
A22	2010	Canada	Cohort	IV
A23	2010	France	Descriptive	VI
A24	2010	Holland	Descriptive	VI

A25	2010	Cuba	Descriptive	VI
A26	2010	Spain	Descriptive	VI
A27	2010	Australia	Descriptive	VI
A28	2010	Sweden	Cohort	IV
A29	2010	Canada	Descriptive	VI
A30	2010	Holland	Descriptive	VI
A31	2010	USA	Descriptive	VI
A32	2011	Canada	Descriptive	VI
A33	2011	France	Cohort	IV
A34	2011	Finland	Descriptive	VI
A35	2011	Brazil	Descriptive	VI
A36	2011	Brazil	Descriptive	VI
A37	2011	Germany	Cohort	IV
A38	2011	Mexico	Descriptive	VI
A39	2011	Brazil	Descriptive	VI
A40	2011	Paquistan	Descriptive	VI
A41	2011	Brazil	Descriptive	VI
A42	2011	Holland	Cohort	IV
A43	2011	Holland	Cohort	IV
A44	2011	Finland	Cohort	IV
A45	2011	Finland	Cohort	IV
A46	2011	France	Descriptive	VI
A47	2011	Brazil	Descriptive	VI
A48	2012	Israel	Cohort	IV
A49	2012	Brazil	Descriptive	VI
A50	2012	Norway	Descriptive	VI
A51	2012	Norway	Descriptive	VI

Figure 1. Characterization of the studies regarding the year of publication, site, type of study and level of evidence.

The participant population of the analyzed research was composed by adults or exclusively elderly and the main scopes are the description of the user profile or the default of use of benzodiazepines; an

estimated prevalence of use; and evaluating their consequences in different populations. The classification of studies according to the main objective, location and population are presented in Table 2.

Main Objective (Number of the Studies)	Place of the Study (Number of studies)	Study population (Number of the studies)
Profile/use pattern (22)	Germany (1), Australia (1), Brazil (6), Canada (2), Chile (1), Cuba (1), France (2), Holland (1), México (3), Norway (3), Sweden (1)	Adults (14) Elderly (8)
Prevalence of consumption (13)	Australia (2), Austria (1), Brazil (2), Spain (2), Finland (2), Holland (2), Israel (1), Paquistan (1)	Adults (9) Elderly (4)
Consequences of the use (10)	Canada (2), Spain (1), USA (1), Finland (1), France (3), Holland (2)	Adults (2) Elderly (9)
Motivation for use (4)	Brazil (1), France (1), Holland (1), Taiwan (1)	Adults (4)
Consequences of interruption (1)	Sweden (1)	Adults (1)
Adherence to drug therapy (1)	Canada (1)	Adults (1)

Figure 2. Characterization of the studies regarding the main purpose, place and population.

The prevalence of benzodiazepine use ranged from 6,9% to 14% in the general population and among the elderly, this rate increases to 9,2% to 13,8%; and predominantly affects females. Women use on average twice as benzodiazepines than men (Table 3).

Depending on the data source, there is great variation of the participant population studies; involving data it having been collected from at least 1.192 to 30.000

individuals when used secondary data; and 27-749 individuals when individuals were approached directly for interview. It is found that the prevalence is on average 12% in studies with primary source, slightly higher than the average of 9,1% for studies with secondary source.

Study e Local	Population	Data source	N	Prevalence		
				Total (%)	Fem (%)	Male (%)
Romero et al. 2008. Spain	Individuals of both sexes with more than 15 years of age in chronic use of BZD.	Secondary	6.885	6,9	9,7	4,0
Assem-Hilger et al. 2009. Áustria	The elderly of both sexes with 75 years of age.	Primary	500	13,8	-	-
Ricci-Cabello et al. 2010. Espanha	Individuals of both sexes of 16 or more years of age.	Secondary	29.478	9,8	-	-
Iqbal et al. 2011. Paquistão	Individuals of both sexes with more than 18 years of age.	Primary	749	14,0	17,0	9,0
Kantorski et al. 2011. Brasil	Individuals of both sexes and of all ages.	Secondary	1.162	10,7	-	-
Telles-Filho et al. 2011. Brasil	Elderly of 60 or older.	Primary	27	9,2	-	-

Figure 3. Characterization of the studies regarding the location, population, data source, sample, total prevalence and by gender.

In view of the epidemiologic transition, there was a trend towards increased use of benzodiazepines ranging from 2,8% to 22%. The elderly, a trend is observed the increased use of these drugs, which reaches up to 17% of this population stratum. Exception to this trend was reported in the Australian study,

which was cited 2,0% decrease in the prevalence of benzodiazepine users due to the establishment of a control and rational use program. In Table 4 the studies on the changes in the consumption of benzodiazepines over time in different populations are shown.

Study and place	Population	Data Source	N	Prevalence		
				I* (%)	II** (%)	Variation (%)
Smith et al. 2009. Austrália.	Individuals of both sexes more than 15 years of age	Secondary	5.000	-	-	-2,0
Ravera et al. 2010. Holanda.	Individuals of both sexes aged 18 and 89 years old.	Secondary	500.000	34,6 21,2	30,2 18,4	4,2*** 2,8****
Smith et al. 2010. Austrália	Individuals of both sexes of more than 15 years of age.	Secondary	-	-	-	22,0
Wittkamp et al. 2010. Holanda.	Individuals of both sexes and of all ages.	Secondary	1.500.000	-	-	14,0
Desplenter et al. 2011. Finlândia	Elderly of 75 or older.	Primary	1.382	-	31,3	17,0
Rikala et al. 2011. Finlândia.	Elderly of 75 or older.	Primary	700	-	31,0	17,0
Blumstein et al, 2012. Israel.	Elderly of 75 or older.	Primary	780	22,2	25,4	3,2

Figure 4. Characterization of the studies regarding the location, population, data source, sample, prevalence found and variations among them.

Prevalence I: refers to the prevalence measured at the time of the initial study.
**Prevalence II: refers to the prevalence measure at the end of the study, independent of the number of measurements during follow-up.
*** Variation in the prevalence of anti-anxiety drugs.
****Variation in the prevalence of hypnotics and sedatives.

Diazepam is the drug most widely used class of benzodiazepines in different populations, reaching from 7,2% to 37% of patients. With regard to the time of use, it is clear that prolonged use is increasing with ageing. In two studies conducted in the Canadian general population the number of individuals with chronic use of these drugs grew by 3,2%. Chronic use of benzodiazepines is also related to unsuccessful attempts to

discontinue the use of drugs of this class. The self-medication report ranged from 24% to 88% of users.

Another aspect investigated was the adherence to drug treatment. When initiating treatment, nonadherence rates decline to advancing age and the leading cause of abandonment are the complaints of forgetfulness or memory impairment especially when using anxiolytics. Many

Wanderley TC, Santos SC.

benzodiazepines are classified as Potentially Inappropriate Medications (PIM) for the elderly. Improper medicines are used by 18% up to 32% of the elderly who participated in the studies analyzed.

Regarding the dependence on benzodiazepines, studies in Mexico, France and Canada, using DSM-IV, estimated that 48,7%, 35,2% and 9,5% of the studied population were dependent respectively. However, when participants in the Canadian study were asked whether they considered themselves dependent, 43% of seniors responded positively. This means that on average 43% of respondents consider themselves dependent on these drugs.

DISCUSSION

The discussion will be presented by means of analytical categories that emerged after acute reading of the articles and descriptive analysis of the results.

♦ General characteristics of the studies

The selected studies show the prevalence of cross designs with a quantitative approach. The use of secondary data from the Health Information Systems, covering epidemiological, administrative and clinical information, is being increasingly employed in research and evaluation in health, in isolation, or integrated, and primary data sources.¹⁵ Despite the use of databases provide broad population coverage and low costs, Coeli et al pointed out some limitations of this research strategy such as: the questions become limited to the available data; the reliability of data; and in the case of administrative bases, not knowing the rules that govern those systems and their changes over time.¹⁵

♦ The use of benzodiazepines in numbers

The analysis of data from studies of general adult population shows a trend towards increased use of benzodiazepines. The progressive decrease humanity's resistance to tolerate stress, profuse introduction of new drugs and the growing propaganda pressure from the pharmaceutical industry, or even inappropriate prescribing habits by physicians may have contributed to the increased use of these drugs.¹⁶ However, Smith et al in a study conducted in Australia reported a reduction of their use in the general population around 2,0%. This reduction was explained by the implementation of effective control policies on the delivery and improvement of prescriptions made by doctors, particularly for the elderly.¹⁷

Use of benzodiazepines and their implications...

Diazepam is the most widely used benzodiazepine and also the most prescribed drug in this class inappropriately, it is estimated that a prescription in ten is inadequate, ie 10% of diazepam users should not make use of it or make use wrongly. According to his statement, also out increased consumption of anxiolytics and decreased use of benzodiazepines as hypnotics.¹⁸ The prescription of hypnotics should be precise and short, taking into account their beneficial and side effects, the etiology of this sleep disorder and, in essence, the patient's age. Traditional benzodiazepines cause more psychomotor adverse reactions during the day than non-benzodiazepines present, as zolpidem, zaleplon and zolpiclone, especially when dealing with elderly and, in some studies, it is observed a trend in substitution of benzodiazepines.¹⁹

♦ Practice of use of benzodiazepines and their consequences

Regarding the practice of self-medication, in studies involving European populations there was the story of the practice of self-medication because of greater control over the prescription and dispensing of medicines in the region. However, in studies done in Paquistão²⁰ and Cuba²¹, the authors report that 24% and 88%, respectively, of the user population of benzodiazepines are self-medicated denoting ineffective control people's access to these drugs and high frequency of incorrect prescriptions.

The predominant use by older women can be explained by the higher prevalence of psychiatric illness among women and their greater frequency in the health services. Furthermore, the aging own changes, such as normal reduction of sleep time, can induce the use of benzodiazepines as hypnotics for the resolution of the picture.⁵ Linked to use there is the inadequacy of prescribing this class of drugs for the elderly causing side effects and drug interactions with serious consequences²²; more likely to fall²³; fractures²⁴; increased cognitive impairment, especially of memory.²⁵

The adherence to drug therapy is defined as the degree to which the patient follows the doctor's advice, or professional consulting health, returns to service and maintain the indicated treatment.¹ With regard to the accession of treatment with benzodiazepines non-membership fees decrease the advancing age and the leading cause of abandonment are the complaints of forgetfulness or memory impairment especially when it is used anxiolytics.²⁶

Wanderley TC, Santos SC.

Use of benzodiazepines and their implications...

The memory impairment is one of the serious consequences of inappropriate use of benzodiazepines.²⁵ In addition, they promote high rates of tolerance and dependence, which leads respectively to an increase of the dose required for the same therapeutic effect and, when its use is stopped abruptly, causing the appearance of signs and symptoms contrary to the expected therapeutic effects of the drug.^{26 27} The effect of the reliance must be widely prevented by the physician through the use of minimum dosages; by treatment periods as short as possible; and by careful patient selection, avoiding prescribe these drugs to patients with a history or prone to drug.²⁸

Chronic use of benzodiazepines flees the recommendations for the rational use of medicines. In general, treatment with benzodiazepines should be very limited over time and do not justify the use of these drugs for long periods except in specific situations such as in some Epileptical frames.⁵ In this regard, it is important to reassess the treatment to prevent chronic and indiscriminate use of these drugs. However, often reassessment is not done systematically and only occurs revenue distribution for the acquisition of medicines.²⁹ The chronic use is also related to failed attempts to discontinue the use of drugs of this class. According to Patten et al³⁰ discontinuation decreased by advancing the use of time, preventing this process which in 90% of chronic users, there is the occurrence of anxiety symptoms when the drug withdrawal which makes it increasingly difficult this process.

CONCLUSION

Most of the studies analyzed aimed to understanding the users' profile, the pattern of use of benzodiazepines and the prevalence in populations; however, gaps remain to be filled as, for example, clarifying the charges or other factors related to the use, possible influences of environmental factors, problems related to the use, performance of professional orientation of correct usage; and costs related to its use. This may have happened as a result of the method employed in the studies or the descriptors used for preparation of this review.

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Wanderley TC, Santos SC.

Use of benzodiazepines and their implications...

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